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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,594	06/22/2000	Irina Nazarenko	0942.4980002/RWE/SEZ	8750

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,594	NAZARENKO ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 9, 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-22,47 and 56-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-22,47 and 56-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 9, 2004 has been entered.

Status

Claims 10-22, 47 and 56-75 are pending.

Claims 10-22, 47 and 56-75 are rejected.

2. Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." Here, the new limitation of "Wherein said detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to said one or more oligonucleotides." in each of the independent claims appears to represent new matter. A careful review by the examiner of all of the cited pages in the specification failed to identify any support for this new negative limitation. The cited portion of page 10, reproduced below, does not indicate that there is no energy transfer, only that there are not two different labels.

Second, they allow detection of the amplification or synthesis product directly, by incorporating the labeled oligonucleotide into the product. Third, they do not require labeling of oligonucleotides with two different compounds (like FRET-based methods), and thus, simplify the production of the labeled oligonucleotides.

The cited portions of pages 70 and 71, reproduced below, also provide no teaching that excludes a transfer of energy.

In this method fluorescent signal is generated upon the incorporation of the specifically labeled primer into the PCR product. The method does not require the presence of any specific quenching moiety or detection oligonucleotide. In some preferred embodiments, the detection oligonucleotides are capable of forming a hairpin structure and are labeled with fluorescein attached close to the 3'-end.

As shown in Fig. 2, in case of internally labeled Oligo A (SEQ ID NO:1), a fluorescence signal increases as a result of presence of the non-labeled complementary oligonucleotide. That means the signal increase was caused by the formation of the double-stranded structure. In contrast, when the fluorescein was present on the 5'-end of the same sequence (Oligo B (SEQ ID NO:2)), fluorescence signal decreased upon hybridization.

In fact, the phrase "not the result of a transfer of energy" was not found by the examiner in the specification.

As noted by MPEP 2173.05(I), " Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

In concert with Grasselli, it is noted that the specification does not even appear to have contemplated this exclusion. For example, the specification notes "[T]he label is any moiety which undergoes a detectable change in any observable property upon hybridization (see page 44, lines 4-6)". This quote expressly supports the position that the specification contemplated any label with any property, including a label which was an acceptor. Further supporting this position is the express statement on page 24, lines 15-16 that "In another embodiment of the invention, the label is a member of a FRET pair."

Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

5. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the term "not the result of a transfer of energy between two different compounds" in the claims. In particular, there is no definition of this phrase in the specification and no mention of the phrase was even found in the specification. The simplest definition, that there is no transfer of energy whatsoever, would not make sense in this context because detection of the label and changes in the label due to hybridization, necessarily must involve transfer of information, which is a form of energy. So even if the claim is read as intended by Applicant, it makes no sense because a single label attached to DNA must have some change due to the hybridization, or it could not be used for the detection at all. This change must involve some transfer of energy between the DNA and label. Therefore, this limitation appears to vitiate the apparent preferred embodiment, as well as the previously cited prior art.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 68-70, 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Livak et al (WO 96/15270).

Livak teaches a method for the quantitation of a target nucleic acid molecule in a sample (abstract and page 14, lines 14-16) comprising:

hybridizing one or more detectably fluorescently labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see page 14, lines 3-28 and page 30, "Hybridization assay using Oligonucleotide probe" and table 7, where Livak teaches hybridization involving the use of probes such as A1-7 which has an internal TAMRA) and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see page 10, lines 16-30, page 34, table 7, where Livak clearly shows that internally labeled probes A1-7, A3-6, P2-7, P510 all show a change in fluorescence between the single and double stranded states)

and quantifying the amount of the target nucleic acid molecules (see page 14, lines 3-28 and page 31, lines 4-6 "The magnitude of RQ indicates the level of hybridization of the A1-26 probe and thus is a measure of the amount of amplified beta-actin DNA segment captured in each well (so Table 7 which provides RQ data for internally labeled probes A1-7, A3-6, P2-7, P510 also measures the amount of target).

Livak expressly meets the proviso that the labeled oligonucleotides do not comprise an acceptor molecule but only involve quenching (see page 10, lines 16-18).

Livak expressly teaches monitoring of PCR amplification using the claimed probes (see page 15, lines 1-15) and exemplifies such a monitoring on page 32 (see subheading "Method for monitoring PCR amplification using oligonucleotide probe") which includes all the components necessary for PCR (see page 32).

Livak teaches the use of hairpin probes (see page 2).

Livak teaches placement of the label at the 3' end, as well as 5 nucleotides and 8 nucleotides from the 3' end (see page 22, probe A1).

8. Claim 71 is rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) and, in view of the 112, second paragraph rejection above, for purposes of this rejection, the term "acceptor" is interpreted to be limited to the sort of acceptors used in Heller, which reemit the fluorescence energy for detection at a different wavelength.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al in view of Nazarenko et al.

Heller teaches a method for the detection of a target nucleic acid molecule in a sample (abstract and column 4) comprising:

hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see figures 2A, 2B, 3A, 3B and column 23, lines 15-29 for examples of oligonucleotides with detectable labels located internally which are also near the 3' or 5' termini) and said one ore more labels

undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see column 25, lines 62-66, where Heller shows that there is no energy transfer at 90 C, when there is no double stranded molecules but that upon cooling and rehybridization to reform the double stranded energy transfer system, there is a change in observable properties in that energy transfer is restored), and

detecting the presence or absence of one or more target nucleic acid molecules (column 17, line 45 to column 19, line 56) which may include a PCR amplification step thereby incubating the nucleic acid mixture to synthesize additional nucleic acid (see column 21, lines 32-35).

Heller teaches the use of Fluorescein and Rhodamine (see Table 2 and column 11).

Heller teaches the location of the acceptor fluorophore within 20 nucleotides of the 3' end (see column 23, line 15). Heller also shows the use of fluorescein, a detectable label, on column 26, line 24, which is 6 nucleotides from the 3' termini.

Heller does not teach the use of hairpin primers in the PCR reaction, nor does Heller teach placement of the fluorophores either four or five nucleotides from the 3' terminus.

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close to the 3' end respectively, wherein the oligonucleotide undergoes a

detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Heller detection method using PCR with a hairpin primer as taught in the Nazarenko method since Heller states "A multiple donor system comprised of such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications (column 10, lines 23-27)". Thus, an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce background to as low a level as possible. Nazarenko provides motivation to combine with Heller, stating that "The main advantage of this method is the generation of the fluorescent signal by the product itself, rather than by the hybridized probe, as in previous methods. This keeps background low and allows real-time quantification of the amplified DNA over an extremely wide dynamic range (page 2521, column 1)".

Thus, an ordinary practitioner seeking to achieve a system with as minimal a background as possible for diagnostic uses in order to detect nucleic acids associated with diseases or infections would have been motivated to use the primer of Nazarenko because Nazarenko expressly states that this primer keeps background low as desired by Heller, who uses multiple fluorophores to relay energy transfer to also keep background low. An ordinary practitioner would have been motivated to form such a multiple relay system of Heller, combined into the hairpin primer of Nazarenko, in order to yield an even further reduced background, thereby further improving the sensitivity and low background of the resultant assay, making it more suitable for detection of nucleic acids for diagnostic purposes.

12. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c)

detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) and, in view of the 112, second paragraph rejection above, for purposes of this rejection, the term "acceptor" is interpreted to be limited to the sort of acceptors used in Heller, which reemit the fluorescence energy for detection at a different wavelength.

Nazarenko does not teach each possible location of the internal base.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

Response to Arguments

13. Applicant's arguments filed February 9, 2004 have been fully considered but they are not persuasive.

Applicant has amended the claims to avoid the new matter rejection and argues that the amendment itself is not new matter. As noted above, the new claim limitations are new matter.

The prior art rejections over the claims rejected under new matter are withdrawn since the prior art does not address the new matter. Removal of the new matter would result in reimposition of these prior art rejections.

Applicant argues that Livak does not teach internal labels. The claim uses the open term "comprising". Livak has internal labels and labels which are not internal. However, as MPEP 2111.03 notes "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps." Therefore, Livak remains an appropriate 102 rejection. A similar argument applies to the other prior art rejections.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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